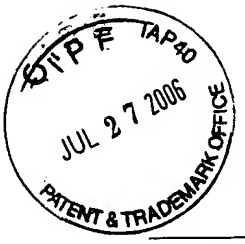
IFW

Application No.: 10/564,367 Docket No.: 1261-0162PUS1



Docket No.: 1261-0162PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Hiroyuki OSADA et al.

Application No.: 10/564,367 Confirmation No.: 9208

Filed: March 23, 2006 Art Unit: 1614

For: THERAPEUTIC AGENT FOR HYPERCALCEMIA AND BONE DISEASE Examiner: Not Yet Assigned

LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Subsequent to the filing of the above-identified application on March 23, 2006, attached hereto is an English translation of the International Preliminary Report on Patentability (Form PCT/IB/338 and 373) and of the Written Opinion of the International Searching Authority (Form PCT/ISA/237) that should be made of record in the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or to credit any overpayment to Deposit Account No. 02-2448 for any

DRN/khm

additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: July 27, 2006

Respectfully submitted,

By _____

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Attachment(s)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL
OF COPIES OF TRANSLATION
OF THE INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY
(CHAPTER I OR CHAPTER II
OF THE PATENT COOPERATION TREATY)
(PCT Rules 44*bis*.3(c) and 72.2)

To:

KAWAGUCHI, Yoshiyuki
Acropolis 21 Building 6th floor 4-10, Higashi
Nihonbashi 3-chome
Chuo-ku
Tokyo, 1030004
JAPON

Date of mailing *(day/month/year)*	
01 June 2006 (01.06.2006)	
Applicant's or agent's file reference RFH1629C4114	**IMPORTANT NOTIFICATION**
International application No. PCT/JP2004/010125	International filing date *(day/month/year)* 15 July 2004 (15.07.2004)
Applicant RIKEN et al	

1. **Transmittal of the translation to the applicant.**

☑ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).

☐ The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

2. **Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

None

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Yoshiko Kuwahara
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 90 90

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference RFH1629C4114	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2004/010125	International filing date *(day/month/year)* 15 July 2004 (15.07.2004)	Priority date *(day/month/year)* 15 July 2003 (15.07.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant RIKEN		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 22 May 2006 (22.05.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Yoshiko Kuwahara Telephone No. +41 22 338 90 90

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference RFH1629C4114	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/010125	15.07.2004	15.07.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant
RIKEN

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/010125

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/010125

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 2, 4	YES
	Claims	3	NO
Inventive step (IS)	Claims		YES
	Claims	1-4	NO
Industrial applicability (IA)	Claims	1-4	YES
	Claims		NO

2. Citations and explanations:

Document 1: SHIMIZU, Takeshi et al., "Chemical modification of reveromycin A and its biological activities," Bioorganic & Medicinal Chemistry Letters, 2002, 12(23), p. 3363-3366

Document 2: NAGAI, Kazuo, "Application of molecular probes for studying the process of differentiation and expression of biological functions of the cells participating in bone metabolism," Nippon Nogei Kagaku Kaishi, 2001, 75(2) p. 111-119

Document 3: JP 7-223945 A (Snow Brand Milk Products Co. Ltd.) 22 August 1995

Document 4: WOO, J. et al., "Reveromycin A induces apoptosis in activated osteoclasts, not in inactived," Journal of Bone and Mineral Research, 2001, Volume 16, Suppl. 1, p. S383

Document 5: WOO, J. et al., "Reveromycin A induces osteoclast apoptosis and inhibits bone resorption," Journal of Bone and Mineral Research, 1999, Volume 14, Suppl. 1, p. S360

<Novelty>

Document 1 describes a reveromycin A derivative wherein the hydroxyl group at position 5 is acetylated (page 3365, Compound 6).

Therefore, based on the description in document 1, the invention of claim 3 lacks novelty and an inventive step.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V.

<Inventive Step>

[A] Claims 1, 2, and 4

Document 1 describes a reveromycin A derivative wherein the hydroxyl group at position 5 is acetylated or *tert*-butyl dimethyl silylated (page 3365, Compounds 6 and 7).

On the other hand, documents 2-5 state that reveromycin A can be used as a remedy to treat hypercalcemia or bone disease.

Generally speaking, this examination finds that in the field of pharmaceuticals it is common practice for persons skilled in the art to confirm the pharmacological action of derivatives of drug compounds to obtain compounds that are more desirable from the standpoint of efficacy, adverse reactions, and the like. Therefore, confirming the anti-hypercalcemia effects or anti-bone disease effects of the derivatives of reveromycin A described in document 1 is merely common practice for persons skilled in the art.

Moreover, in reviewing the experimental results in Example 1 of the specification of this application, when the ratio of the ED_{50} values for the apoptosis inducing activity of Compounds 2 and 27 with respect to mature osteoclasts and RAW264 cells is compared with that of natural reveromycin A, this examination does not find that the activity of Compounds 2 and 27 is more selective for mature osteoclasts than the activity of natural reveromycin A, and in looking at the other explanations in the specification, it is impossible to verify that the inventions of the various claims of this application provide a markedly superior effect in comparison to the inventions described in the various documents above.

Therefore, based on the descriptions in documents 1-5, the inventions of claims 1, 2, and 4 lack an inventive step.

[B] Claim 4

Document 1 describes a reveromycin A derivative wherein the hydroxyl group at position 5 is acetylated (page 3365, Compound 6). In addition, document 1 proposes that even though this derivative has almost no I1eRS inhibitory activity, it exhibits a morphological reversion effect on src^{ts}-NRK cells, and this is because the derivative is hydrolyzed to the active form by an esterase in the cells (page 3366, left column, lines 6 to 1 from the bottom).

On the other hand, documents 2-5 state that reveromycin A can be used as a remedy to treat hypercalcemia or bone disease.

This being the case, this examination finds that based on the descriptions in these documents, persons skilled in the art can easily conceive of using a reveromycin A derivative described in document 1 as a reveromycin A prodrug for the treatment of hypercalcemia or bone disease with the expectation that it will be hydrolyzed to reveromycin A, which is the active form in the body.

Moreover, just as in [A] above, this examination finds no particularly outstanding effect is provided thereby.

Therefore, based on the descriptions in documents 1-5, the invention of claim 4 lacks an inventive step.